REMARKS

Applicants have cancelled Claim 27 without prejudice to, or disclaimer of, the subject matter contained therein. Applicants maintain that the cancellation of a claim makes no admission as to its patentability and reserve the right to pursue the subject matter of the cancelled claim in this or any other patent application.

Applicants have amended Claim 22 to read "specifically binds." Applicants maintain that the amendments add no new matter and are fully supported by the specification as originally filed. For example, support for the amendment to Claim 22 can be found in the substitute specification in original Claim 18.

Claims 22-26 are presented for examination. Applicants respond below to the specific rejections raised by the Examiner in the Office Action mailed September 8, 2004. For the reasons set forth below, Applicants respectfully traverse.

Rejection under 35 U.S.C. §101 – Utility

The PTO has rejected the pending claims under 35 U.S.C. § 101 as lacking patentable utility. The PTO concedes that the cited utilities are credible. However, the PTO alleges that the invention lacks both substantial and specific utility. Applicants respectfully disagree.

Substantial Utility

The PTO argues that the invention lacks substantial utility because the level of overexpression in cancer cells of the nucleic acid which encodes the PRO539 protein was minimal, and there is no evidence that overexpression is significant or a real effect and not simply produced by chance. In addition, the PTO argues that the invention lacks utility because the overexpression of the nucleic acid is not relevant to the utility of the protein and antibodies and there is no evidence that the protein is overexpressed. The PTO cites three references to support its position that there is no *necessary* correlation between gene amplification, gene expression, and protein expression. The PTO concludes that because there is no *necessary* connection between the amount of DNA in a cell and the amount of mRNA, and no *necessary* connection between the level of protein in a cell and the amount of mRNA, any evidence of overexpression of one component does not provide utility for the protein. The PTO argues that the current situation closely tracks Example 12 of the Utility Guidelines, because where there is

no *necessary* relationship between the protein levels or utilities and a small level of mRNA overexpression in cancer cells, the invention lacks any "real world" context of use for PRO539.

Utility – Legal Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic tool without also identifying the condition that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient,* at least with regard to defining a 'substantial' utility." (M.P.E.P. § 2107.01, emphasis added).

Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Utility need NOT be Proved to a Statistical Certainty – a Reasonable Correlation between the Evidence and the Asserted Utility is Sufficient

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the

art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). *See, also In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977). Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

In *Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996), the Court of Appeals for the Federal Circuit upheld a PTO decision that *in vitro* testing of a novel pharmaceutical compound was sufficient to establish practical utility, stating the following rule:

> [T]esting is often required to establish practical utility. But the test results **need not absolutely prove** that the compound is pharmacologically active. All that is required is that the tests be "*reasonably* indicative of the desired [pharmacological] response." In other words, there must be **a sufficient correlation** between the tests and an asserted pharmacological activity so as to convince those skilled in the art, **to a reasonable probability**, that the novel compound will exhibit the asserted pharmacological behavior." *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996) (internal citations omitted, bold emphasis added, italics in original).

While the *Fujikawa* case was in the context of utility for pharmaceutical compounds, the principals stated by the Court are applicable in the instant case where the asserted utility is for a therapeutic and diagnostic use – utility does not have to be established to an absolute certainty, rather, the evidence must convince a person of skill in the art "to a reasonable probability." In addition, the evidence need not be direct, so long as there is a "sufficient correlation" between the tests performed and the asserted utility.

The Court in *Fujikawa* relied in part on its decision in *Cross v. Iizuka*, 753 F.2d 1040, 224 U.S.P.Q. 739 (Fed. Cir. 1985). In *Cross*, the Appellant argued that basic *in vitro* tests conducted in cellular fractions did not establish a practical utility for the claimed compounds. Appellant argued that more sophisticated *in vitro* tests using intact cells, or *in vivo* tests, were necessary to establish a practical utility. The Court in *Cross* rejected this argument, instead favoring the argument of the Appellee:

> *[I]n vitro* results...are generally predictive of *in vivo* test results, i.e., there is a **reasonable correlation** therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are. [Appellee] has not urged, and rightly so, that there is an invariable exact correlation between *in vitro* test results and *in vivo* test results. Rather, [Appellee's] position is that successful *in vitro* testing for a particular pharmacological activity establishes a **significant probability** that *in vivo* testing for this particular pharmacological activity will be successful. *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739 (Fed. Cir. 1985) (emphasis added).

The *Cross* case is very similar to the present case. Like *in vitro* testing in the pharmaceutical industry, those of skill in the field of biotechnology rely on the reasonable correlation that exists between gene expression and protein expression (see below). Were there no reasonable correlation between the two, the techniques that measure gene levels such as microarray analysis, differential display, and quantitative PCR would not be so widely used by those in the art. As in *Cross*, Applicants here do not argue that there is "an invariable exact correlation" between gene expression and protein expression. Instead, Applicants' position detailed below is that a measured change in gene expression in cancer cells establishes a "significant probability" that the expression of the encoded polypeptide in cancer will also be changed based on "a reasonable correlation therebetween".

Taken together, the legal standard for demonstrating utility is a relatively low hurdle. An Applicant need only provide evidence such that it is **more likely than not that a person of skill**

in the art would be convinced, to a reasonable probability, that the asserted utility is true. The evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. The Applicant **does not need to provide evidence such that it establishes an asserted utility as a matter of statistical certainty.**

Even assuming that the PTO has met its initial burden to offer evidence that one of ordinary skill in the art would reasonably doubt the truth of the asserted utility, Applicants assert that they have met their burden of providing rebuttal evidence such that it is more likely than not those skilled in the art, to a reasonable probability, would believe that antibodies to the PRO539 polypeptide are useful as a diagnostic tool for cancer.

Applicants have established that the Gene Encoding the PRO539 Polypeptide is Amplified in Lung and Colon Tumors compared to Normal Tissue and is Useful as a Diagnostic Tool

Applicants first address the PTO's argument that the level of overexpression of nucleic acid encoding PRO539 was minimal and insignificant. Applicants submit that the gene amplification data provided in the present application are sufficient to establish a specific and substantial utility for the gene encoding the PRO539 polypeptide, as well as the PRO539 polypeptide.

Applicants previously submitted the declaration of Dr. Audrey Goddard with exhibits A-G. In her declaration, Dr. Goddard states that a 2-fold increase in gene copy number, i.e., a ΔCt ΔCt value of 1, is "significant and useful" in detecting cancerous tumors or the diagnosis of cancer. Goddard Declaration, paragraph 7. The nucleic acid encoding the PRO539 polypeptide has a value of 1 or greater in several tumor samples tested. Thus, the differential expression of the nucleic acid encoding PRO539 can be used to distinguish cancerous tissue from normal tissue.

In the present Office Action, the PTO has not offered *any* reason to reject Dr. Goddard's declaration. Applicants remind the PTO that the applicant need **not** provide evidence such that it establishes an asserted utility "as a matter of statistical certainty." M.P.E.P. at § 2107.02, part VII (2004). Applicants therefore submit that using well-accepted, standard techniques, they have established that the gene amplification data reported in Example 16 are significant, and the utility for the PRO539 DNA in distinguishing between normal and cancerous tissue has been

established. For the reasons discussed below, this leads to utility for antibodies to the PRO539 polypeptide as well.

Applicants have established that the Accepted Understanding in the Art is that there is a Reasonable Correlation between Gene Amplification and Overexpression of the Encoded Protein

Applicants next address the PTO's argument that the invention lacks utility because the overexpression of the nucleic acid is not relevant to the utility of the protein, and there is no evidence that the protein is overexpressed. The PTO cites Pennica *et al.* (Proc. Natl. Acad. Sci. (1998) 95:14717-14722) for the proposition that there is no *necessary* connection between the amount of DNA in a cell and the amount of mRNA in a cell. The PTO also cites Meric *et al.* (Molecular Cancer Therapeutics (2002) 1:971-79) and Gokman-Polar (Cancer Research (2001) 61:1375-81) to support its position that there is no *necessary* correlation between mRNA levels and protein levels. The PTO concludes that because there is no *necessary* connection between gene amplification and mRNA, and between mRNA and protein, any evidence of overexpression of one component does not provide utility for the protein.

As discussed above, evidence of utility does not have to be to an absolute certainty, and therefore there does not need to be a *necessary* connection between gene amplification and protein expression. Rather, there need only be a *reasonable* correlation between the evidence offered and the asserted utility such that it is more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true.

The teachings in Genes V, a leading textbook in the field, illustrate that at the time the instant application was filed, it was well known by those of skill in the art that gene amplification leads to overexpression of the corresponding gene product. Benjamin Lewin, Genes V, 5th ed. 1994, pages 1196-1201, submitted herewith as Exhibit 1. In a section entitled "Insertion, translocation, or amplification may activate proto-oncogenes", the text describes various molecular events that lead to overexpression of a gene product, using the *c-myc* gene as an example. The first mechanism taught is insertion of a retrovirus upstream of the gene which causes it to be driven by a more efficient promoter, resulting in increased mRNA and protein levels. Next, Lewin teaches that chromosomal translocations may bring a gene to a new region where it is actively expressed, resulting in increased gene and protein expression. The third mechanism whereby protein levels of oncogenes are overexpressed is gene amplification. The

text emphasizes that the common thread among the different means of activation of proto-oncogenes is that the expression of the gene is increased. Thus, as of 1994, it was well-known in the art that gene amplification is correlated with overexpression of the corresponding mRNA and encoded protein.

Additional information regarding the understanding of those of skill in the art regarding the relationship between gene amplification and protein overexpression at the time the instant application was filed is found in Alitalo (Med. Biol., 62:304-317 (1984), submitted herewith as Exhibit 2), and Merlino *et al.* (J. Clin. Invest., 75:1077-1079 (1985), submitted herewith as Exhibit 3). Under the heading "Enhanced Expression of Amplified Oncogenes," Alitalo states that "[i]n all cases where they have been studied, the amplified oncogenes have been found abundantly expressed at the mRNA level, roughly in proportion to the amount of DNA amplification (see Table 1)." Alitalo at 313 (emphasis added). Table 1 lists eleven examples of amplified oncogenes where expression levels were examined. In all eleven cases, expression of the amplified oncogene was elevated. Thus, Alitalo clearly teaches that amplification leads to overexpression. Merlino *et al.* studied epidermoid carcinoma cells, and teach that amplification of the EGF receptor gene results in increased levels of EGF receptor mRNA and increased levels of EGF receptor protein. Taken together, the excerpt from Genes V, as well as the Alitalo and Merlino references, establish that as of the filing date of the instant application, those of skill in the art appreciated the correlation between gene amplification and overexpression of the encoded gene product.

The teachings of Genes V, Alitalo, and Merlino are confirmed in several more recent reports that also document the correlation between gene amplification and levels of protein. Applicants submit herewith two more recent studies providing evidence that the teachings referred to above are still widely accepted by those of skill in the art. Orntoft *et al.* (*Molecular and Cellular Proteomics*, 1:37-45 (2002); submitted herewith as Exhibit 4) studied transcript levels of 5600 genes in malignant bladder cancers which were linked to a gain/loss of chromosomal material using an array-based method. Orntoft *et al.* showed that there was a gene dosage effect and teach that "in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts." Orntoft at 37, column 1, abstract. In addition, Hyman *et al.* (*Cancer Research*, 62:6240-6245 (2002); submitted herewith as Exhibit 5) used CGH analysis and cDNA microarrays to compare DNA copy

numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines. They showed that there is "evidence of a prominent global influence of copy number changes on gene expression levels." Hyman at 6244, column 1, last paragraph.

Additional supportive teachings are also provided by Pollack *et al.* (*PNAS*, 99:12963-12968 (2002); submitted herewith as Exhibit 6) who studied a series of primary human breast tumors and found that "[b]y analyzing mRNA levels in parallel, we have also discovered that *changes in DNA copy number have a large, pervasive, direct effect on global gene expression patterns* in both breast cancer cell lines and tumors." Pollack at 12967 at column 1, emphasis added. Their study found that "62% of highly amplified genes show moderately or highly elevated expression, that DNA copy number influences gene expression across a wide range of DNA copy number alterations (deletion, low-, mid- and high-level amplification), that on average, a 2-fold change in DNA copy number is associated with a corresponding 1.5-fold change in mRNA levels." (Pollack at 12963, column 1, abstract).

Bahnassy *et al.* (BMC Gastroenterology, 4:22-34 (2004), submitted herewith as Exhibit 7) studied the amplification of *cyclin D1, cyclin A, histone H3* and *Ki-67*, and assessed the levels of the encoded proteins by immunohistochemistry. Bahnassy *et al.* found a "significant correlation between *cyclin D1* gene amplification and protein overexpression" (Bahnassy at 27, column 1). Similarly, Blancato *et al.* (British Journal of Cancer, 90(8), 1612-1619 (2004), submitted herewith as Exhibit 8), report that overexpression of *c-myc* mRNA and c-Myc protein is related to the copy number of the *c-myc* amplification (Blancato at 1613, column 2). Bahnassy and Blancato demonstrate continued evidentiary support for the widely-accepted principle that gene amplification correlates with overexpression of the encoded protein.

Together, these excerpts and articles collectively teach that *it is more likely than not* that gene amplification increases mRNA expression. This evidence establishes that there is a reasonable correlation between gene amplification and gene expression, and one of skill in the art would believe, to a reasonable probability, that gene amplification would lead to increased gene expression.

Relying on a single contrary example of one gene, the PTO states that the literature reports that it does not *necessarily* follow that an increase in gene copy number results in increased gene expression and increased polypeptide expression. The PTO focuses on a statement from the abstract of Pennica that the *WISP-2* gene DNA was amplified in colon

tumors, but RNA expression was reduced. Pennica at 14717. This inverse correlation is in contrast to the *WISP-1* gene, which was amplified and had higher RNA levels. The authors of Pennica offer an explanation for what they obviously viewed as an anomalous result: "Because the center of the 20q13 amplicon [of which *WISP-2* is a part] has not yet been identified, it is possible that the *apparent amplification* observed for *WISP-2* may be caused by another gene in this amplicon." *Id.* at 14722, emphasis added. Thus, the example of a lack of positive correlation between gene amplification and RNA levels relied on by the PTO may be an artifact. The fact that the authors attempt to explain this anomaly only supports Applicants' argument that the accepted understanding in the art is that there is a direct correlation between gene amplification and an increase in gene expression.

As stated above, the standard for utility is not absolute or even statistical certainty, but rather whether one of skill in the art would be more likely than not to believe the asserted utility. Even if Pennica supported the PTO's argument, which it does not, one contrary example is not sufficient to prove that a person of skill in the art would have a reasonable doubt that gene amplification is not correlated to gene expression. Given the evidence provided by the Applicants which establishes that there is a reasonable correlation between gene amplification and mRNA expression, one of skill in the art would believe, to a reasonable probability, that the reported amplification of the PRO539 gene would lead to an increase in the level of PRO539 mRNA.

Applicants next address the PTO's argument that there is no *necessary* correlation between mRNA levels and protein levels.

Applicants have previously submitted a copy of a Declaration by J. Christopher Grimaldi, an expert in the field of cancer biology. As stated in paragraph 5 of the declaration, "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be overexpressed." Similarly, the previously submitted declaration of Paul Polakis, Ph.D., an expert in the field of cancer biology states that "it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein." Polakis Declaration, paragraph 6. He cites as supporting evidence not only his years of personal experience, but also results from experiments related to the present application. He reports that for the mRNAs

overexpressed in cancer that have been examined, 80% had correspondingly higher levels of the encoded protein. Polakis Declaration at paragraphs 4 and 5.

The statements of Grimaldi and Polakis are supported by the teachings in Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of the Cell (3rd ed. 1994) (submitted herewith as Exhibit 9) and (4th ed. 2002) (submitted herewith as Exhibit 10)). Figure 9-2 of Exhibit 9 shows the steps at which eucarotic gene expression can be controlled. The first step depicted is transcriptional control. Exhibit 9 provides that "[f]or most genes transcriptional controls are paramount. This makes sense because, of all the possible control points illustrated in Figure 9-2, only transcriptional control ensures that no superfluous intermediates are synthesized." Exhibit 9 at 403 (emphasis added). In addition, the text states that "Although controls on the initiation of gene transcription are the predominant form of regulation for most genes, other controls can act later in the pathway from RNA to protein to modulate the amount of gene product that is made." Exhibit 9 at 453 (emphasis added). Thus, as established in Exhibit 1, the predominant mechanism for regulating the amount of protein produced is by regulating transcription initiation.

In Exhibit 10, Figure 6-3 on page 302 illustrates the basic principle that there is a correlation between increased gene expression and increased protein expression. The accompanying text states that "a cell can change (or regulate) the expression of each of its genes according to the needs of the moment – *most obviously by controlling the production of its mRNA*." Exhibit 10 at 302 (emphasis added). Similarly, Figure 6-90 on page 364 of Exhibit 10 illustrates the path from gene to protein. The accompanying text states that while potentially each step can be regulated by the cell, "the initiation of transcription is the most common point for a cell to regulate the expression of each of its genes." Exhibit 10 at 364 (emphasis added). This point is repeated on page 379, where the authors state that of all the possible points for regulating protein expression, "[f]or most genes transcriptional controls are paramount." Exhibit 2 at 379 (emphasis added).

Further support for Applicants' position can be found in the textbook, Genes VI, (Benjamin Lewin, Genes VI (1997)) (submitted herewith as Exhibit 11) which states "having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming

majority of regulatory events occur at the initiation of transcription." *Genes VI* at 847-848 (emphasis added).

Additional support is also found in Zhigang *et al.*, World Journal of Surgical Oncology 2:13, 2004, submitted herewith as Exhibit 12. Zhigang studied the expression of prostate stem cell antigen (PSCA) protein and mRNA to validate it as a potential molecular target for diagnosis and treatment of human prostate cancer. The data showed "a high degree of correlation between PSCA protein and mRNA expression" Exhibit 12 at 6. Of the samples tested, 81 out of 87 showed a high degree of correlation between mRNA expression and protein expression. The authors conclude that "it is demonstrated that PSCA protein and mRNA overexpressed in human prostate cancer, and that the increased protein level of PSCA was resulted from the upregulated transcription of its mRNA." Exhibit 12 at 11. Even though the correlation between mRNA expression and protein expression occurred in 93% of the samples tested, not 100%, the authors state that "PSCA may be a promising molecular marker for the clinical prognosis of human Pca and a valuable target for diagnosis and therapy of this tumor." *Id.*

Finally, Applicants submit the Declaration of Victoria Smith, Ph.D., an expert in the field of Molecular Biology, originally submitted in the related and co-pending application Serial No. 10/032,996 (submitted herewith as Exhibit 13). Dr. Smith states that Exhibit B of her Declaration reports the results of the microarray analysis conducted on the gene encoding PRO539 (DNA47465) as part of the investigation of several newly discovered DNA sequences. The results indicate that the gene encoding PRO539 is significantly overexpressed in eight of the twenty-six lung tumor samples tested compared to the normal lung tissue controls. That is the equivalent of nearly one in every three samples (31%). In addition, four out of five squamous cell lung carcinomas (80%) are significantly overexpressed (shown in bold). In contrast, only one of the seven individual normal lung tissue samples shows significant overexpression of the PRO539 gene (14%).

Dr. Smith states that "[i]t is well-established in the art that overexpression of the mRNA for a gene is likely to lead to overexpression of the corresponding protein." Smith Declaration at paragraph 6. She explain that:

> While not every lung tumor sample tested shows overexpression of the PRO539 gene, the data in Exhibit B indicate that a significant portion of lung tumors do (30% of all lung tumors tested and 80% of squamous cell tumors tested), while only one of the normal lung tissue samples shows overexpression

> (14%). Given the known correlation between overexpression of a gene and the corresponding overexpression of the encoded protein, it is very likely that a similar number of lung tumors will overexpress the PRO539 protein, while very few normal lung tissue samples likely will. Together with the data reported in Example 16 that the gene encoding PRO539 is amplified in some lung tumors, including squamous cell lung carcinoma, the results reported in Exhibit B indicate that the PRO539 gene and protein, as well as antibodies to the encoded protein, can be used to differentiate some cancerous lung tissue, particularly squamous cell carcinoma, from normal lung tissue. Smith Declaration at paragraph 7 (emphasis in original).

Because not all lung tumors show overexpression of PRO539, it cannot be used to exclude a sample being tested as non-cancerous. However, the PRO539 gene, protein, and corresponding antibodies are useful as a diagnostic tool for lung cancer, particularly squamous cell carcinoma, since a very high percentage of squamous cell lung carcinomas overexpress the gene and most likely the encoded protein, while very few normal lung samples do.

Together, the declarations of Grimaldi, Polakis, and Smith, the accompanying references and data, and the excerpts and references provided above all establish that the accepted understanding in the art is that there is a reasonable correlation between changes in gene expression and the level of the encoded protein. Applicants have provided microarray data showing the increased expression of the gene encoding PRO539 in a significant portion of lung tumors, and have established that there is a reasonable correlation between expression of the gene and the level of PRO539 protein.

In arguing against this assertion, the PTO cites two references. The PTO relies on a statement from Gokman-Polar that "PKC mRNA levels do not directly correlate with PKC protein levels." Office Action at 3-4. However, a close review of the entire article indicates that with one exception, the trend in the data is that mRNA and protein levels are positively correlated, supporting Applicants assertion. In Figure 2, the protein level of two isozymes shows a decrease, while the third is increased. This same pattern is seen for the corresponding mRNA levels in Figure 6, although admittedly the increase in mRNA for the third isozyme is minimal. Similarly, comparing the protein levels of the three isozymes in Figure 4 to the corresponding mRNA levels in Figure 7, with one exception the mRNA levels are positively correlated to protein levels. While protein levels do not increase or decrease in direct proportion to the changes in mRNA, the trend in five of the six examples is that protein levels are positively correlated to mRNA levels. This evidence is hardly sufficient to establish that one of skill in the

art would reasonably doubt that there is a reasonable correlation between mRNA levels and protein levels.

The Meric article cited by the PTO offers even less support for the PTO's position. The PTO relies on the statement that "Gene expression is quite complicated, however, and is also regulated at the level of mRNA stability, mRNA translation, and protein stability." Office Action at 3. What the PTO ignores is the preceding statement by the authors:

> The **fundamental principle** of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells...[M]ost efforts have concentrated on identifying differences in gene expression at the level of mRNA, which can be attributable to either DNA amplification or to differences in transcription. Meric at 971 (emphasis added).

This statement supports Applicants' asserted utility. It is true that there is no *necessary* correlation between gene expression and protein expression because there are other mechanism for regulating gene expression. However, were there no significant correlation between gene expression and protein levels, exploiting differences in gene expression between cancer cells and normal cells would not be a "fundamental principle of molecular therapeutics in cancer."

In light of the lack of support for the PTO's argument, Applicants submit that the PTO has failed to establish a reason for one of skill in the art to doubt the asserted utility. Even if it has, Applicants have offered sufficient evidence to rebut the PTO's argument and establish that there is a reasonable correlation between gene amplification, gene expression, and protein expression. The PTO is again reminded that an absolute or even statistical certainty is not required. Applicants have established that it is more likely than not that one of skill in the art would be convinced, to a reasonable probability, that the PRO539 protein is overexpressed in certain cancers, and therefore antibodies to the PRO539 protein have utility as a diagnostic tool.

The Instant Case Differs Significantly from Example 12 of the Utility Guidelines

Applicants next address the PTO's argument that the current situation closely tracks Example 12 of the Utility Guidelines, because where there is no necessary relationship between the protein levels or utilities and a small level of mRNA overexpression in cancer cells, the invention lacks any "real world" context of use for PRO539.

In Example 12, the specification discloses a protein, receptor A, which is the binding partner for protein X. The specification does not characterize the isolated protein with regard to

its biological function or any disease or body condition that is associated with the isolated protein. In addition, the function of protein X has also not been identified. One of the asserted utilities for receptor A is making monoclonal antibodies to receptor A which can be used as a therapeutic drug to effect control over the receptor. In the analysis of this asserted utility for receptor A, the Utility Guidelines state that "since neither the specification nor the art of record disclose *any* diseases or conditions associated with receptor A, the asserted utility in this case essentially is a method of treating an unspecified, undisclosed disease or condition, which does not define a 'real world' context of use." Utility Guidelines at 66, emphasis added.

The situation in Example 12 is not the situation here. Applicants have demonstrated that the nucleic acid encoding PRO539 is amplified and overexpressed in certain cancers. Thus, unlike the protein in Example 12, PRO539 **is** associated with a known disease or condition – more specifically, lung and colon cancer.

The PTO asserts that because it is the nucleic acid, and not the PRO539 polypeptide, which has been shown to be amplified in cancer cells, the PRO539 polypeptide is not associated with any disease. However, as discussed at length above, Applicants have demonstrated a reasonable correlation between gene amplification, gene expression, and protein expression such that one of skill in the art would believe, to a reasonable probability, that the PRO539 protein is overexpressed in certain cancers and therefore antibodies to PRO539 are useful as a diagnostic tool.

The present situation closely resembles the caveat discussed at the end of Example 12, where receptor A is shown to be present on the cell membranes of melanoma cells but not on the cell membranes of normal skin cells. The Utility Guidelines state that in that situation, "making a monoclonal antibody to receptor A for diagnosing melanoma would constitute a well-established utility." Utility Guidelines at 70. Similarly, here Applicants have provided evidence that it is more likely than not that the PRO539 polypeptide is expressed at higher levels in certain cancer cells than normal tissue, including additional microarray data showing that the PRO539 gene is overexpressed in certain tumors. Because the PRO539 polypeptide is overexpressed in certain tumors, it can be used to make diagnostic antibodies.

The PTO's rejection of Applicants' expert declarations as "fundamentally flawed" because they fail to provide specific evidence regarding PRO539 is unwarranted. As discussed above, specific evidence of overexpression of PRO539 in cancer is not required. Instead, indirect

evidence of the asserted utility of the PRO539 polypeptide can be offered so long as there is a "reasonable correlation" between the proffered evidence and asserted utility, such that it is more likely than not that a person of skill in the art would believe the asserted utility. Applicants have provided data showing amplification of the gene encoding PRO539 in lung and colon cancer, as well as data showing overexpression of the PRO539 gene in lung cancer. Applicants' expert declarations establish a reasonable correlation between gene amplification, gene expression, and protein expression. In view of the data, these declarations support the asserted utility of antibodies to PRO539 as a diagnostic tool for cancer.

Similarly, the PTO's reliance on *In re Kirk*, 376 F.2d 936, 153 U.S.P.Q. 48 (C.C.P.A. 1967) is also misplaced. In *Kirk*, the asserted utility for the claimed compounds was "a new class of compounds often possessing high biological activity" and "intermediates in the preparation of compounds with valuable biological properties...". *Id.* at 1120, 1121. The Court rejected these statements as "nebulous expressions" of usefulness. *Id.* at 1124.

Here, Applicants have asserted a much more specific utility than "biological activity" or "biological properties." Applicants have provided evidence of amplification and overexpression of the gene encoding PRO539 in certain cancers and have shown that this evidence is reasonably correlated to overexpression of the PRO539 polypeptide in those same cancers, namely, lung and colon cancer. As Example 12 of the Utility Guidelines make clear, when a protein is differentially expressed in cancer compared to normal tissue, the protein and antibodies have utility in diagnosing the cancer. This is the situation here.

Specific Utility

The PTO argues that even if substantial utility were found, there is no specific utility given for antibodies to the PRO539 protein, since antibodies to the protein, as distinguished from the nucleic acid, have not been associated with any disease, condition, or any other specific feature. Relying on the lack of correlation between levels of nucleic acid and protein cited in the Gokman-Polar and Meric references, the PTO argues that the overexpression of the nucleic acid gives no specific utility because it is entirely unrelated to uses of the protein or antibody. Applicants respectfully disagree.

Specific Utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention."

M.P.E.P. § 2107.01, part I (2004). Applicants submit that the evidence of amplification and overexpression of PRO539 nucleic acids in certain types of cancer cells along with the declarations and references discussed above provide a specific utility for the claimed antibodies. As stated above, Applicants have established a reasonable correlation between gene amplification, gene expression, and protein expression. This makes antibodies to the PRO539 protein useful in diagnosing lung and colon cancer. This is not a general utility that would apply to the broad class of antibodies.

The amplification and overexpression of PRO539 nucleic acid in certain cancer cells distinguishes this case from Examples 4 and 12 of the Utility Guidelines cited by the PTO. In both examples, there is no description of the protein beyond its sequence or its binding of an unidentified ligand. Here, the disclosed proteins are encoded by a nucleic acid that is amplified and overexpressed in certain cancer cells, which is reasonably correlated to overexpression of the PRO539 polypeptide. This makes the utility of using antibodies to the protein to diagnose lung and colon cancer specific, since in general, antibodies are not specific to proteins that are overexpressed in cancer cells.

The PTO's previous response to Applicants' arguments regarding specific utility is lacking. The PTO asserts that because Applicants' arguments presume the PRO539 protein is overexpressed, and this is not *necessarily* the case, this cannot serve as the foundation to support specific utility. However, utility need not be established "beyond a reasonable doubt" or to a "statistical certainty." Rather, Applicants need only establish that the asserted utility is "more likely than not." M.P.E.P. at § 2107.02, part VII (2004). Thus, it need not be shown that overexpression of PRO539 polypeptide is *necessarily* the case, only that it is more likely than not, which Applicants have done.

Conclusion

Given the totality of the evidence provided, Applicants submit that they have established a credible, substantial, and specific utility for the claimed antibodies as diagnostic tools. According to the M.P.E.P. and case law cited above, irrefutable proof of a claimed utility is **not** required. Rather, a specific and substantial credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants have offered sufficient evidence to

establish that there is a reasonable correlation between gene amplification, gene expression, and protein expression. Applicants remind the PTO that:

> A small degree of utility is sufficient . . . The claimed invention must only be capable of performing some beneficial function . . . An invention does not lack utility merely because the particular embodiment disclosed in the patent lacks perfection or performs crudely . . . A commercially successful product is not required . . . Nor is it essential that the invention accomplish all its intended functions . . . or operate under all conditions . . . partial success being sufficient to demonstrate patentable utility . . . In short, **the defense of non-utility cannot be sustained without proof of total incapacity**. If an invention is only partially successful in achieving a useful result, a rejection of the claimed invention as a whole based on a lack of utility is not appropriate. M.P.E.P. at 2107.01 (underline emphasis in original, bold emphasis added, citations omitted).

Applicants have established that it is more likely than not that one of skill in the art would be convinced, to a reasonable probability, that based on the gene amplification and gene expression submitted herewith for the PRO539 gene, the PRO539 protein is overexpressed in lung and colon cancers, and therefore antibodies to PRO539 have utility as a diagnostic tool for these cancers. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejection under 35 U.S.C. §112 – Enablement

The PTO rejected Claims 22-27 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. The PTO cites *In re Wands* and the factors set forth therein to determine the scope of enablement. However, Applicants respectfully submit that the PTO's conclusions are inconsistent with the teachings of *Wands*, as they rest on the erroneous assumption that a *necessary* connection between gene amplification and protein expression is required. The PTO states that "[w]ith regard to enablement, fundamentally the same arguments [as those given for utility] apply, and this rejection is maintained for the same reasons as given above in response to the arguments on utility." Office Action at 15.

The Applicants believe that the evidence, declarations, references, and arguments discussed above make clear that Applicants have established that it is more likely than not that one of skill in the art would be convinced, to a reasonable probability, that the PRO539 protein is overexpressed in certain cancers, and therefore antibodies to PRO539 have utility as a diagnostic

tool. To the extent that the enablement rejection is based on a lack of utility, Applicants respectfully request that the PTO reconsider and withdraw the enablement rejection under 35 U.S.C. §112.

As amended, the pending claims are related to an antibody that specifically binds to the polypeptide of SEQ ID NO:7. Applicants submit that the claimed antibodies are enabled, as one of skill in the art would know how to make and use them. The techniques for the creation of antibodies are well known and routine in the art, and the use of the claimed antibodies as a diagnostic tool is disclosed in the application, for example at page 95, lines 9-21 of the substitute specification. Thus, at least one use of antibodies to the PRO539 polypeptide is adequately enabled, which is all that is required – "if any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention." M.P.E.P. 2164.01(c). In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the enablement rejection under 35 U.S.C. § 112, first paragraph.

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: March 7, 2005

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